

## **REMARKS**

By the present communication, claims 93 is amended, and claims 104 and 107 are canceled. New claims 110-111 are added. No new matter is introduced as the amended claim language is supported by the application as filed. Claims 93-103, 105-106, and 108-111 are now pending. Applicants respectfully request that the Examiner reconsider the application in view of the foregoing amendments and the remarks that follow.

### **I. Rejections Under 35 U.S.C. § 112, First Paragraph**

#### **A. Enablement**

Applicant respectfully traverses the rejection of claims 93-109 under the first paragraph of 35 U.S.C. § 112 for allegedly failing to comply with the enablement requirement. The cancellation of claim 104 and 107 renders the rejection of these claims moot. With respect to the remaining claims, Applicants respectfully submit that an analysis of the factors set forth by the Federal Circuit show that the claims are enabled for at least the following reasons.

First, the breadth of the claims and nature of the invention support enablement as the claims are narrowly tailored to subject matter supported by the working examples in the application and the skill and knowledge in the art. Second, the Office has failed to establish that state of the art and the level of unpredictability in the art are so highly unpredictable as to negate Applicants' evidence of enablement. Third, the extensive number of working examples and confirmatory data, including extensive in vivo data, provide sufficient guidance to fully support enablement of the claims. Fourth, in view of the previous factors, the amount of experimentation needed to practice the full scope of the claims is not undue and therefore also supports enablement of the claims. Accordingly, Applicants submit that the claims are enabled under 35 U.S.C. § 112, first paragraph, and request that the present ground of rejection be withdrawn.

*1. The Breadth of the Claims and the Nature of the Invention Support Enablement of the Claims*

Applicants respectfully submit that the breadth of the present claims and the nature of the invention supports enablement of the claims. Contrary to assertions in the Office Action (page 7, lines 3-4), the claims are not directed to the treatment of any disease mediated by tyrosine kinases or all cancers, or even a "long list of cancers" (page 4, lines 5-6). In fact, as amended, independent claim 93 is clearly directed to the treatment of a limited set of cancers using the structurally related group of compounds of Structure I. Moreover, claims 105, 106, and 108-109 (as well as new claims 110-111) recite subsets of these cancers and claims 103 and 108-109 (as well as new claim 111) recite a specific compound of Structure I (4-amino-5-fluoro-3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one, hereinafter compound 166). As discussed below, the present application discloses biological activity data for every cancer recited in claim 93 and for many of the compounds. Thus, none of the claims are unreasonably broad and certain claims, such as 103 and 108-109 (as well as new claim 111), closely track the working examples.

Moreover, the claims are closely aligned with and commensurate with the scope of the disclosure. First, as set forth in Applicants' previous responses, the application discloses how to make the compounds of Structure I; describes over 1400 compounds actually made; discloses how to test the compounds for inhibitory activity with respect to numerous receptor tyrosine kinases (RTKs); and shows that hundreds of these compounds display such activity. Reply of 10/11/2007, p. 13; Reply of 3/16/07, pp. 32-33. More importantly, the *in vivo* data disclosed in the application and discussed below provide extensive evidence of the anti-cancer properties of compounds of Structure I, particularly for compound 166. Reply of 10/11/2007, pp. 14-17; Reply of 3/16/07, pp. 33-36.

Because the breadth of the claims are commensurate with the disclosure and the focused nature of the claims, Applicants respectfully submit that these factors support the enablement of

claims 93-103 and 105-106 and 108-109. Likewise, these factors also support enablement of new claims 110-111.

2. *The State of the Art and the Level of Predictability in the Art Support Enablement of the Claims*

The Office maintains that the state of the art is unpredictable and the level of unpredictability is high. Regarding the state of the art, the Office asserts that “[t]here is no absolute predictability even in view of the seemingly high level of skill in the art.” Action, p. 4, lines 9-10. Regarding the level of predictability in the art, the Office asserts that “the instantly claimed invention is highly unpredictable since one skilled in the art would recognize that in regards to the therapeutic effects of all diseases, whether or not the modulation of tyrosine kinase c-Kit or other specific receptors would make a difference in the disease.” *Id.*, p. 6, lines 5-8. Finally, the Office asserts that “in the absence of a showing of a nexus between any and all known diseases and the modulation of a specific tyrosine kinase receptor, one of ordinary skill in the art is unable to fully predict possible results from the administration of the compound of claim 1 due to the unpredictability of the role of modulation of tyrosine kinase specific receptors.” *Id.*, lines 8-12. In support of these assertions, the Office relies on Freshney (*Culture of Animal Cells, A Manual of Basic Technique*, Alan R. Liss, Inc., 1983, New York, p. 4) and Dermer (*Bio/Technology*, 1994, 12:320) to show the predictability of the art. *Id.*, pp. 5-6; 6/11/07 Office Action, pp. 10-11.

Applicants respectfully disagree with each of these assertions for at least two reasons. First, the Office mischaracterizes the legal standard for enablement as it relates to unpredictability in the art. Second, the Freshney and Dermer references fails to support its findings regarding the state and predictability of the art.

(a) *The Office mischaracterizes the legal standard for enablement as it relates to unpredictability in the art.*

Patent law regarding enablement is clear. Statute requires that the specification enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to

make and use the invention. 35 U.S.C. §112, first paragraph. The Federal Circuit has ruled that “the term ‘undue experimentation’ does not appear in the statute, but it is well established that enablement requires that the specification teach those in the art to make and use the invention without undue experimentation.” *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). Whether undue experimentation is required to practice a claimed invention may be assessed using a variety of factors, among them the state of the art and the level of unpredictability in the art. *Id.* Such factors are evaluated based on pertinent facts and no more is required.

Consequently, there is no basis in law requiring Appellant to demonstrate “a nexus between any and all known diseases and the modulation of a specific tyrosine kinase receptor” to demonstrate enablement of the claimed invention or to show that the art is not highly unpredictable. In fact, the Office fails to cite a basis in statute, rule or binding court precedent for requiring a showing of nexus or explaining what constitutes such a showing. Moreover, even though “there is no absolute predictability even in view of the seemingly high level of skill in the art,” Applicants are not required to show absolute predictability or to exemplify every claimed embodiment, but merely to show that the claimed invention may be practiced without undue experimentation. Unpredictability in an art may be overcome, e.g., by guidance and working examples in the application and known or demonstrated correlations between working examples and claimed methods.

*(b) The Office’s reliance on Freshney and Dermer fails to support its findings regarding the state and predictability of the art.*

The two articles cited by the Office fail to establish the state or predictability of the art with regard to the claimed invention. Regarding Freshney, which has been cited in each of the Office Actions of record, the reference is a 1983 book chapter disclosing alleged short-comings of tissue culture from 25 years ago. See 12/21/07 Office Action, pp. 4-5; 6/11/07 Office Action, pp. 5-6; 9/18/06 Office Action, pp. 5-6. Due to its age, the reference cannot provide information as to the state of the art at the time of filing (2003) and lacks any specific information regarding the cancer cell lines used by Applicants. The more recent Dermer reference (9 years prior to the filing date), cited in the 6/11/07 Office Action, p. 10, allegedly teaches that tissue culture of

cancer cells is a poor representation of malignancy, but again fails to point out specific shortcomings in any cancer cell culture used by Applicants. Such dated and non-specific prior art cannot support the Office's contention that the art is "highly unpredictable," nor the Office's implication that Applicant must exemplify every embodiment that falls within the claims.

In fact, as set forth in Applicants' prior Replies (3/16/2007 and 10/11/2007), inhibitors of various RTKs associated with particular types of cancer have been shown to inhibit cancer growth *in vitro* and *in vivo*. Applicants submit that, as detailed below, the present application provides abundant data showing that the presently claimed compounds also inhibit RTKs associated with the claimed cancers and inhibit the growth of such cancers *in vitro* and *in vivo*.

3. *The Amount of Direction Provided and the Existence of Working Examples in the Application Support Enablement of the Claims*

Applicants respectfully submit that the application provides ample guidance for practicing the claimed methods without undue experimentation. As set forth in Applicant's Replies of 3/16/07, pp. 32-36, and 10/11/07, pp. 14-17, the application provides copious guidance regarding the synthesis, test procedures, and use of the recited compounds. In addition, as discussed in the previous replies and set forth in more detail below, the application contains extensive data demonstrating the biological activity of the claimed compounds and, including 1) tyrosine kinase inhibition data for a majority of the 1400 compounds synthesized with a wide range of kinases (paragraph 729); 2) more detailed tyrosine kinase inhibition data for the compound of example 166 (paragraph 752); 3) anticancer activity of compound 166 in all 27 cancer cell lines tested (paragraph 753-54 and Table 6); and 4) *in vivo* anticancer activity, including activity against human cancer xenografts and *in vivo* antiangiogenic activity (paragraphs 760-766). Despite all of the evidence to the contrary in the application, the Office maintains that "these tests do not show enablement that all of the listed cancers of claim 93 are treatable by the instant markush." Action, p. 8.

Applicants respectfully disagree for at least two reasons. First, the Office's implication that Applicants must provide *in vivo* data for each of the compounds and cancers recited in claim

93 is inconsistent with the legal standard for enablement. Second, in misconstruing this legal standard, the Office continues to ignore the considerable guidance for practicing the claimed methods provided in the application.

As outlined in Section I.A.2.(a), above, the law regarding enablement requires only that the application teach those in the art to make and use the invention without undue experimentation. There is no basis in law that enablement may only be shown for the claimed methods by human or *in vivo* data. Indeed, “a rigorous or invariable exact correlation [between *in vitro* or *in vivo* animal model assays and a claimed method] is not required” to show enablement. MPEP §2164.02, citing *Cross v. Iizuka*, 753 F.2d 1040, 1050 (Fed. Cir. 1985). Consistent with this standard, the MPEP acknowledges that “if a particular [*in vitro* or *in vivo*] model is recognized as correlating to a specific condition, then it should be accepted as correlating unless the examiner has evidence that the model does not correlate. MPEP 2164.02. As noted above, the Office has failed to provide such evidence. As shown below, even if the Office had produced such evidence, the data in the application support any necessary correlation and enable one of ordinary skill in the art to practice the claimed invention.

The present application contains extensive biological data in support of the claimed methods, including cancer inhibition data for every cancer recited in claim 93 and its dependent claims. The application further contains *in vivo* cancer inhibition data for the majority of cancers recited in the claims and demonstrates correlations between the *in vitro* and *in vivo* data. Finally, the application evidences correlations between *in vitro* kinase inhibition and the anticancer activity of claimed compounds. All of this data, the correlations, as well as Applicants’ confirmatory post-filing papers are discussed below.

For hematologic cancers, including acute myelogenous leukemia, chronic myelogenous leukemia, and acute lymphoblastic leukemia, the data in Table 6 show that a claimed compound, compound 166, inhibited the proliferation of nine blood cancer cell lines with an  $EC_{50}$  of less than 10  $\mu$ M. The lines tested (by the procedure given in paragraph 753) provide a representative sample of hematologic cancers and include ARH-77 (plasma cell leukemia), K562 (myelogenous

leukemia), KU812 (chronic myelogenous leukemia), MOLT4 (acute lymphoblastic leukemia), MV4-11 (acute myelogenous leukemia), RS4;11 (acute myelogenous leukemia), TF-1 (myelogenous leukemia), HL60 (promyelocytic leukemia), and M-NFS-60 (murine leukemia). The specification further discloses at paragraph 754 that the compound displayed an  $EC_{50}$  of 13 nM against MV4-11 and 510 nM against RS4;11, both acute myelogenous leukemic cell lines. Thus, the application demonstrates the anticancer activity of a claimed compound for each of the three recited hematologic cancers as well as hematologic cancers in general.

Furthermore, the anti-cancer activity observed in these leukemia cell lines correlates with *in vivo* data provided in the application. Paragraph 761 and Figures 11-13 show the *in vivo* anti-cancer activity of compound 166 against the hematologic cancer, acute myelogenous leukemia (AML). Human MV4-11 tumor cells were implanted in the flank of irradiated SCID-NOD mice. Tumors were then allowed to grow to 300, 500, or 1000 mm<sup>3</sup> before treatment was initiated with daily oral dosing at 30 mg/kg/day. Compound 166 displayed an  $ED_{50}$  of 4 mg/kg/day in this tumor model in SCID-NOD mice (FIG. 11), and a dose of 30 mg/kg/day inhibited the growth of larger MV4-11 tumors by 86% for tumors of 500 mm<sup>3</sup> volume at start of treatment and by 80% for tumors of 1000 mm<sup>3</sup> volume at start of treatment (FIG. 12). Several complete regressions were also observed. Regressions were found to be stable after cessation of dosing. In those tumors that recurred, a second cycle of 30 mg/kg/day dosing of the compound again caused partial regression, indicating a lack of acquired resistance to the compound. Cyclic dosing regimes also proved effective *in vivo* against this tumor type (FIG. 13). Finally, compound 166 delayed disease progression in mice bearing disseminated human leukemia cells and prolonged survival time. See Applicants' previously submitted post-filing article, Lopes de Menezes, D.E. *et al.*, Clin. Cancer Res. 2005; 11 (14) 5281-91, at p. 5287 and FIG. 6A.

Thus, it is clear that the inhibition of AML *in vivo* by a compound of the claimed invention correlates with the *in vitro* inhibition of AML observed in cell culture. That this correlation is recognized by those of skill in the art is supported by the ongoing clinical trials of

compound 166 for AML (see p. 17 of Applicants' reply, dated 10/11/2007, and Lopes de Menezes *et al.* at page 5290).

With respect to colon cancer, the data in Table 6 of the application show that compound 166 inhibited the proliferation of four colon cancer cell lines (HCT-116, KM12L4A, SW620, HT29) with an EC<sub>50</sub> of less than 10 uM. Proliferation of the KM12L4A cell line by compound 166 was especially potent, displaying an EC<sub>50</sub> of 9 nM. Specification, paragraph 754. Consistent with these results, compound 166 also exhibits *in vivo* activity against colon cancer as explained in the application.

[T]he compound induces regression and growth inhibition in subcutaneous KM12L4a human colon tumor xenografts in *nu/nu* mice. FIG. 1 shows tumor volume over time at various doses of 4-amino-5-fluoro-3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one. Dosing started when tumor xenografts reached 125 mm<sup>3</sup>. The results show significant tumor growth inhibition after 4 doses of greater than or equal to 30 mg/kg, and tumor regressions at 60 and 100 mg/kg. Similar results were observed in 90-100% of animals with larger KM12L4a colon tumor xenografts. Treatment started when tumor size reached 500 and 1000 mm<sup>3</sup>. Specification, paragraph 760

Similar confirmatory *in vivo* data against HCT116 colon cancer xenografts in *nu/nu* mice is found in Applicants' post-filing article, Lee, S.H. et al. Clin. Cancer Res. 2005; 11 (10), 3633-3641 (cited in Applicants' replies dated 3/16/2007 and 10/11/2007), on pp. 3636-38 and Fig. 4.

Compound 166 is also effective alone or in combination with other anticancer drugs against colon cancer *in vivo* as explained in the application at paragraph 767 (see also FIGS. 5 & 6).

Significant potentiation of activity was seen, with the most dramatic effects at low, inactive doses of 4-amino-5-fluoro-3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one as shown in FIG. 5. A cyclic dosing regimen of the compound at 50 mg/kg in combination with irinotecan gave excellent results, with 3 complete regressions and 7 partial regressions, as shown in FIG. 6.



In view of these results, the skilled artisan would once again understand that Applicants have shown a correlation between the *in vitro* and *in vivo* activity of a claimed compound for one of the claimed cancers, *i.e.*, colon cancer.

With respect to another claimed cancer, ovarian carcinoma, Table 6 discloses that compound 166 inhibited proliferation of the ovarian cancer cell line SK-OV-3 with an  $EC_{50}$  of less than 10  $\mu$ M. Furthermore, paragraph 767 describes and FIG. 7 shows that compound 166, alone and in combination with another anticancer agent, inhibits the growth of ovarian cancer xenografts. Thus, the *in vivo* anticancer activity of a claimed compound again tracks the observed *in vitro* anticancer activity of the compound against a claimed cancer.

The specification also presents *in vitro* and *in vivo* data for breast cancer. Table 6 shows three breast cancer cell lines in which compound 166 inhibited proliferation with an  $EC_{50}$  of less than 10  $\mu$ M: 4T1, HMEC and MDA-MB435. As described in paragraph 762, compound 166 proved efficacious in a tumor metastasis study in which 4T1 murine breast tumor cells were implanted subcutaneously in BALB/c mice. Compound 166 inhibited the primary tumor up to 82% and inhibited liver metastases by more than 75% at all doses above 10 mg/kg/d. The *in vivo* anticancer activity thus correlates with the *in vitro* anticancer activity of another cancer recited in the claims.

With respect to prostate cancer, Table 6 shows that proliferation of three prostate cancer cell lines were inhibited by compound 166 with an  $EC_{50}$  of less than 10  $\mu$ M. Lines tested include DU185, PC-3P, and PrEC. Oral dose scheduling studies in were performed in *SCID* mice having subcutaneous PC3 human prostate tumor xenografts as described in paragraph 765. Significant and similar tumor inhibition was observed in all treatment groups as shown in FIG. 3. Yet again, Applicants' data show that *in vivo* anticancer activity of a claimed compound correlates with the *in vitro* anti-cancer activity observed for the same compound.

The specification also discloses in Table 6 that compound 166 inhibits proliferation of two lung cancer cell lines and two pituitary cancer cell lines with an  $EC_{50}$  of less than 10  $\mu$ M. In

view of the excellent correlation between the cell culture data and the *in vivo* data for the five other cancer types provided above, Applicants submit that the skilled artisan could reasonably expect *in vivo* activity for this compound against lung cancer and pituitary cancer, and would know how to test and assess such activity.

Applicants further submit that the *in vivo* and *in vitro* data discussed above in conjunction with additional data from the application support enablement of the full scope of compounds described by the Markush structure in claim 93. Specifically, the application presents data linking the inhibition of therapeutically relevant receptor tyrosine kinases by the claimed compounds to *in vivo* anti-cancer activity of the compounds. First, as noted in paragraph 752, compound 166 displayed IC<sub>50</sub>s of less than 30 nM for nine receptor tyrosine kinases: FGFR1, FGFR3, VEGFR1, VEGFR2, VEGFR3, PDGFR $\beta$ , c-Kit, p60src, and FLT-3. As shown in Applicants' previous replies dated 3/16/2007 and 10/11/2007, one or more of these kinases play a role in each of the claimed cancers. Data in the present application links inhibition of such kinases by the claimed compounds to the observed cell culture and *in vivo* cancer inhibition.

For example, FLT-3 is a receptor tyrosine kinase expressed on and involved in the proliferation of AML cells in both mutated and wild-type forms (see Specification, paragraph 11 and Lopes de Menezes *et al.*, p. 5281.). As noted above, compound 166 potently inhibits this kinase. FLT-3 acts through autophosphorylation and phosphorylation of downstream signaling kinases, ERK and STAT5, which are key proteins in cell survival and proliferation. Data in paragraphs 756 and 757 show that compound 166 inhibits autophosphorylation of FLT-3 in cultured MV4-11 and RS4;11 AML cells and inhibits phosphorylation of its downstream targets, ERK and STAT5 in cultured MV4-11 AML cells. Similarly, the Lopes de Menezes article shows that compound 166 inhibits phosphorylation of ERK and STAT5 in RS4;11 AML cells in culture (p. 5283-84, Figs. 1-2) and in MV4-11 tumors *in vivo* (p. 5285, Fig. 3). Moreover, it was found that the differences in the level of inhibition of downstream phosphorylation between MV4-11 AML cells and RS4;11 AML cells (by compound 166) recapitulated the difference in

anticancer EC<sub>50</sub>s for these cell lines, providing strong evidence that inhibition of FLT-3 correlates with the observed *in vitro* and *in vivo* anticancer activity.

In another example, KM12L4A colon cancer cells express PDGFR $\beta$  and VEGFR1/2 on their surfaces. Specification, paragraph 756. Again, as noted above, compound 166 potently inhibits these kinases. As described in paragraph 756, compound 166 inhibits autophosphorylation of PDGFR $\beta$  and phosphorylation of its downstream target, ERK, in cultured KM12L4A colon cancer cells. Likewise, Sang et al. provides confirmatory data that compound 166 inhibits phosphorylation of PDGFR $\beta$  and ERK *in vivo* in KM12L4A tumors and inhibits phosphorylation of ERK *in vivo* in HCT116 tumors (p. 3636, Table 3, Fig. 3). In the latter paper it is noted that "tumor regression and stabilization in colon tumor models were observed at dose levels (30-100 mg/kg) consistent with those required for target modulation" (p. 3640). Thus, the present application provides further evidence that inhibition of PDGFR $\beta$  and VEGFR1/2 correlates with the observed anticancer activity of a compound of the invention.

Applicants submit that the skilled artisan would understand such correlations extend to the compounds of Structure I in claim 93. Each of the compounds of Structure I share a large core structure with compound 166: 4-amino-3-benzimidazol-2-yl-quinolinone or the closely related 4-amino-3-pyridinoimidazol-2-yl-quinolinone. Applicants have provided over 1400 actual compounds having the core structure of Structure I. The majority of these 1400+ compounds inhibit the same kinases that compound 166 inhibits with IC<sub>50</sub>s of less than 10  $\mu$ M and many with IC<sub>50</sub>s of less than 1  $\mu$ M. Specification, paragraph 729. In view of the common structural relationship between the compounds of Structure I, including compound 166, the common kinase inhibitory activity displayed by the myriad examples of compounds of Structure I, and the extensive, demonstrated correlation between kinase activity and anticancer activity for the recited cancers, Applicants submit that the skilled artisan would reasonably expect inhibition of the disclosed kinases to correlate with *in vivo* anticancer activity for compounds of Structure I.

In summary, the present application contains an enormous amount of data demonstrating the anti-cancer activity of compounds of Structure I for every cancer recited in claim 93 and the

remaining claims. The present application also includes extensive *in vivo* data for every cancer recited in claims 106, 110 and 111. It further provides very specific data for the use of compound 166, the recited compound of claims 103, 108, 109, and 110, in the treatment of the recited cancers. The data repeatedly demonstrate correlations between *in vitro* and *in vivo* anticancer activity for a compound of the invention and evidence a reasonable correlation between inhibition of relevant receptor tyrosine kinases, inhibition of cancer cell proliferation in culture and inhibition of cancer growth *in vivo* for compounds of Structure I. Accordingly, Applicants respectfully submit that the amount of guidance and the existence of working examples in the application strongly support the enablement of the present claims.

4. *The Level of Skill in the Art Supports Enablement of the Claims*

The Office admits that the level of skill in the art is high. Office Action, p. 7, line 10. Therefore, Applicants respectfully submit that this factor supports the enablement of the present claims.

5. *The Quantity of Experimentation Needed Supports Enablement of the Claims*

In view of the scope of the claims and the guidance provided in the application, the quantity of experimentation necessary to practice the claimed invention is not undue. Applicants submit that the Office has impermissibly asserted an unreasonably broad claim scope in assessing the quantity of experimentation needed to practice the invention. Further, the Office has not properly assessed the level of guidance provided in the application in view of the legal standard for the quantity of experimentation.

In assessing the quantity of experimentation needed to practice the invention, the Office has incorrectly construed the breadth of the claims. The Office asserts that undue experimentation is necessary “to determine what diseases out of all known diseases would be benefited by the mediation of tyrosine kinase receptors,” and “to determine which of the claimed compounds would provide treatment of the disease.” Action, p. 7. However, as explained throughout Section I.A., the claims do not recite or encompass all known diseases of tyrosine

kinase receptors. In fact, claim 93 does not mention tyrosine kinase receptors at all but recites instead a limited number of cancers, treatable with compounds of Structure I. The alleged burden of determining which diseases mediated by particular RTKs are treatable with the claimed compounds is simply nonexistent.

Instead, as set forth in Section I.A.(3), extensive procedures and data are disclosed to allow the use of the claimed compounds in treatment of the claimed cancers. Any experimentation needed to practice the claimed methods in view of this disclosure must be assessed by the appropriate legal standard. As observed by the court in *In re Wands*, “[t]he test [for undue experimentation] is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed.” *In re Wands* at 737 (citations omitted). Moreover, “the fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation.” M.P.E.P. § 2164.01 (citing *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int’l Trade Comm’n 1983), *aff’d sub nom.*, and *Massachusetts, Institute of Technology v. A.B. Fortia*, 774 F.2d 1104, 227 USPQ 428 (Fed. Cir. 1985)). Thus, considerable and even complex experimentation is not undue if it is routine in the art.

In the present application, in view of the extensive *in vitro* and *in vivo* data specific for each of the recited cancers and the demonstrated correlations between said data, further testing to establish, e.g., optimization of dosing and treatment protocols will be routine to the art. Moreover, it will not require undue experimentation to determine which of the claimed compounds will be most useful in treating the recited cancers. The working examples demonstrate that a large number of compounds described by Structure I inhibit various RTKs associated with cancer. The extensive *in vitro* and *in vivo* data establish that inhibition of such RTKs reasonably correlate with inhibition of cancer growth. In view of such guidance and the high level of skill in the art, Applicants submit that the quantity of experimentation required to

practice the claimed invention is not undue. Accordingly, Applicants respectfully submit that the quantity of experimentation is not undue, but supports the enablement of the present claims.

In summary, the Wands factors regarding enablement clearly support enablement of the present claims. In view of the breadth of the claims being commensurate with the application, the focused nature of the claims, the lack of support demonstrating that the art is "highly unpredictable," the extensive guidance and working examples provided in the application, and the high level of skill in the art, Applicants respectfully submit that the full scope of the pending claims is enabled. Accordingly, Applicants respectfully request that the enablement rejection be withdrawn.

## **B. Written Description**

Claims 93-109 stand rejected under the first paragraph of 35 U.S.C. § 112 for allegedly failing to comply with the written description requirement. As claims 104 and 107 are canceled, the rejection is moot with respect to these claims. In support of this rejection, the Office asserts that "the instant specification does not adequately describe the nexus between the modulation of the specific tyrosine kinases (i.e. c-Kit among others) and a useful treatment of [each of the cancers recited in claim 93]." Because there is no basis in law for requiring a showing of nexus to demonstrate written description of claimed subject matter and because the claims at issue do comply with the written description requirement, Applicants respectfully request that this ground of rejection be withdrawn.

### *1. Nexus Is Not a Requirement of Written Description Under 35 U.S.C. § 112*

Applicants respectfully submit that there is no basis in law for requiring a showing of nexus to demonstrate written description of claimed subject matter. To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. See, e.g., *Moba, B.V. v. Diamond Automation, Inc.*, 325 F. 3d 1306, 1319, (Fed. Cir. 2003); *Vas-Cath, Inc. v. Mahurkar*, 935 F. 2d 1555, 1563 (Fed. Cir. 1991). An

Applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. *Lockwood v. American Airlines, Inc.*, 107 F. 3d 1565, 1572 (Fed. Cir. 1997). An analysis of compliance with the written description requirement is conducted from the standpoint of one of skill in the art at the time the application was filed. See, e.g., *Wang Labs. V. Toshiba Corp.*, 993 F.2d 858, 865 (Fed. Cir. 1993). There is a strong presumption that an adequate written description of the claimed invention is present when the application is filed. *In re Wertheim*, 541 F. 2d 257, 263 (CCPA 1976). “Consequently, rejection of an original claim for lack of written description should be rare.” M.P.E.P. § 2163 II. A.

In contrast to this case law, the Office fails to support a requirement for nexus with any citation to any statute, rule or binding precedent, nor does it explain what showing meets a nexus requirement. Because the Office has failed to set forth sufficient evidence or reasoning to rebut the presumption that the specification provides an adequate written description of claims 93-109, no *prima facie* case of lack of written description may be established. Nevertheless, as shown below, the present claims satisfy the standard for written description.

2. *Claims 93-109 Comply with the Written Description Requirement Under 35 U.S.C. § 112, First Paragraph*

The written description requirement for a claimed genus may be satisfied through a variety of ways, including a description of sufficient, relevant functional characteristics coupled with a known or disclosed correlation between function and structure. M.P.E.P. §2163 II.A.3.(a) (ii). Specifically, the Federal Circuit has ruled that “the written description requirement would be met for all of the claims [of the patent at issue] if the functional characteristic of [the claimed invention was] coupled with a disclosed correlation between that function and a structure that is sufficiently known or disclosed.” *Noelle v. Lederman*, 355 F.3d 1343 1350 (Fed. Cir. 2004).

Applicants respectfully submit that claims 93-103, 56-106 and 108-109 are supported throughout their scope by the application as filed. Independent claim 93 recites a method of

treating a specific set of cancers by administering compounds of Structure I to a patient. Compounds of Structure I have a common core structure. As discussed in Section I.A.3. above, the working examples show that such compounds inhibit numerous RTKs, that inhibition of such RTKs correlates with anticancer activity in cell culture and with *in vivo* anticancer activity for the specific cancers recited in claim 93. In addition, claims 103, 108, and 109 (as well as 111) are each drawn to a single compound (compound 166) which Applicants have demonstrated to exhibit the claimed anticancer activity (*Id.*, paragraphs 753-767). Thus, the extensive data in the application and confirmatory data in Applicants' post-filing papers supports the conclusion that the inventors were in possession of the claimed invention at the time of filing. Accordingly, Applicants respectfully request that the present written description rejection be withdrawn.

## **II. Rejections Under 35 U.S.C. § 102**

Claims 93-109 stand rejected under 35 U.S.C. § 102(e) as allegedly being anticipated by U.S. Patent Nos. 6,605,617 and 6,800,760, and under 35 U.S.C. § 102(a) as allegedly being anticipated by U.S. Patent No. 6,605,617, WO 2002/0107392 (actually U.S. Patent Publication 2002/0107392) and WO 200222895 (actually WO 200222598). In support of these rejections, the Office notes that “ [the ‘760 patent] teaches that the claimed compounds of ‘760 have angiogenesis or neovascularization properties. Angiogenesis is well expected to halt the growth of cancer cells.” Action, p. 9. As claims 104 and 107 are canceled, the rejection is moot with respect to these claims. Because the cited references fail to teach each and every element of the claimed methods, Applicants respectfully traverse.

First, it is clear that none of the cited references *expressly* disclose any of the specific cancers recited in independent claim 93. Second, because “a prior art reference that discloses a genus still does not inherently disclose all species within that broad category,” the cited references do not *inherently* disclose any of these cancers. Thus, the excerpt of the ‘760 patent cited by the Office is insufficient to establish inherency under well-established case law.



Applicants respectfully direct the Office's attention to MPEP 2112 IV and the cases cited therein, which outline the requirements for rejections based on inherency.

To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.' *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999).

In relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art. *Ex parte Levy*, 17 USPQ2d 1461, 1464 (Be. Pat. App. & Inter. 1990) (emphasis in original).

Clearly, the burden in demonstrating inherency is a high one.

In *Metabolite Labs., Inc. v. Lab. Corp. of Am. Holdings*, the Federal Circuit applied this standard to a fact situation analogous to the present application. *Metabolite Labs*, 71 USPQ2d 1081 (Fed. Cir. 2004). At issue in *Metabolite Labs* was the validity of a claim to a method for detecting a deficiency of cobalamin or folate in a subject comprising the steps of assaying a body fluid for an elevated level of total homocysteine and correlating that level with a deficiency of cobalamin or folate. *Id.* at 1084. The alleged infringer argued that the claim was either anticipated or obvious over a prior art reference disclosing "that total homocysteine should be used to investigate 'perturbations of homocysteine metabolism in humans during disease or pharmacological interventions that affect metabolism of one-carbon compounds.'" *Id.* at 1091. Although the prior art reference did not expressly mention cobalamin or folate deficiencies, these deficiencies were known to constitute just such a perturbation. *Id.* Nevertheless, the Federal Circuit upheld the validity of the claimed method. *Id.* Specifically, the court stated:

Rather than necessarily containing the correlation between homocysteine and cobalamin or folate deficiencies, Refsum [the

prior art reference] simply invites further experimentation to find such associations. An invitation to investigate is not an inherent disclosure... Refsum discloses no more than a broad genus of potential applications of its discoveries. A prior art reference that discloses a genus still does not inherently disclose all species within that broad category." *Id.* (citations omitted, emphasis added).

Similar to the prior art in *Metabolite Labs*, the prior art cited in the present case does not inherently anticipate or render obvious the claimed methods. The cited references do no more than disclose a broad genus of potential applications (the treatment of cancer in general) using inhibitors of a certain class of receptor tyrosine kinases. Accordingly, Applicants respectfully request that the rejections under 35 U.S.C. § 102 be withdrawn.

### CONCLUSION

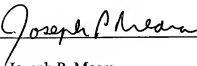
In view of the above remarks, it is respectfully submitted that all rejections have been overcome. Early notice to this effect is earnestly solicited. The Examiner is invited to telephone the undersigned at the number listed below if doing so would be helpful in advancing the application to issue.

Respectfully submitted,

Date June 20, 2008

FOLEY & LARDNER LLP  
Customer Number: 23524  
Telephone: (608) 258-4303  
Facsimile: (608) 258-4258

By



Joseph P. Meara  
Attorney for Applicant  
Registration No. 44,932